Drug Substance	Olaparib (AZD2281, KU-0059436), Durvalumab (MEDI 4736)
Study Number	ESR-15-11311/EPM 6724
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NCT03167619

PHASE II MULTICENTER STUDY OF DURVALUMAB (MEDI4736) AND OLAPARIB IN PLATINUM TREATED ADVANCED TRIPLE NEGATIVE BREAST CANCER - DORA

STUDY CHAIRS

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July 02, 2018

Food and Drug Administration

Center for Drug Evaluation and Research Division
of Cardiovascular and Renal Products 5901-B
Ammendale Road

Beltsville, MD 20705-1266

Attn: Kim Robertson

1 RE: IND 133602 / A0005 • DORA

General Correspondence: Transfer of IND Sponsor

Dear Sir/Madam,

Phase II Multicenter Study of Durvalumab and Olaparib in Platinum treated advanced triple negative breast cancer – DORA is being conducted under the above referenced IND. This is a prospective, randomized, multi-center, safety and efficacy study. No sites have been activated, and no participants have enrolled to the study yet. Study enrollment is expected to begin later this year (estimate August 1st, 2018). The investigational plan is to activate a total of 6 sites (3 US, 2 Korea, 1 Singapore) under this IND.

This is to inform you that, effective July 02, 2018, I, Dr. Danny Benjamin, MD, have transferred all rights for IND 133602 to Dr. Sarah Sammons, MD of Duke University. Dr. Sammons will receive a complete record of the IND.

Sincerely,

Danny
Benjamin, MD
PhD

2 DANIEL K. BENJAMIN, MD, MPH, PHD

Kiser-Arena Distinguished Professor of Pediatrics,
Duke University Faculty Associate Director, Duke
Clinical Research Institute

[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms used in the Clinical Study Protocol.

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Abbreviation or Special term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
bid	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CR	complete response
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
DCI	Duke Cancer Institute
DCO	data cut-off
DCRI	Duke Clinical Research Institute
DNA	deoxy-ribonucleic acid
DSB	double strand breaks
EC	European Commission
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ER	estrogen receptor
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GGT	gamma glutamyltransferase
Hb	Hemoglobin
Hct	Hematocrit

HDPE	**high density polyethylene**
HER2	**human epidermal growth factor receptor 2**
HIV	**human immunodeficiency virus**
HR	**homologous recombination repair**
HRD	**HR deficiency**
IB	**investigator's brochure**
ICF	**informed consent form**
ICH	**International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use**
IEC	**Institutional Ethics Committee**
Ig	**Immunoglobulin**
IHC	**Immunohistochemistry**
IND	**investigational new drug**
INR	**international normalized ratio**
IP	**Investigational Product**
irAEs	**immune-related adverse events**
IRB	**Institutional Review Board**
iRECIST	**RECIST adapted for response with immunotherapeutics**
IV	**Intravenous**
LD	**longest diameter**
LSD	**lysine-specific histone demethylase**
MCH	**mean cell hemoglobin**
MCHC	**mean cell hemoglobin concentration**
MCV	**mean cell volume**
MDS	**myelodysplastic syndrome**
MedDRA	**medical dictionary for regulatory activities**
MRI	**magnetic resonance imaging**
mTNBC	**metastatic triple negative breast cancer**
NCI	**National Cancer Institute**
OAEs	**other significant adverse events**
od	**once daily**

OS	**overall survival**
PARP	**poly (adenosine diphosphate ribose) polymerases**
PD	**progressive disease**
PD-L1	**programmed death ligand-1**
PFS	**progression free survival**
PK	**pharmacokinetics**
PR	**partial response**
Q2W	**dose every 2 weeks**
Q4W	**dose every 4 weeks**
RBC	**red blood cells**
RECIST	**Response Evaluation Criteria in Solid Tumors**
RI	**reticulocyte Index**
RP2D	**recommended phase 2 dose**
SAE	**serious adverse event**
SD	**stable disease**
SGGCP	**Singapore Guideline for Good Clinical Practice**
SSBs	**single strand breaks**
TILs	**tumor-infiltrating lymphocytes**
TNBC	**triple negative breast cancer**
ULN	**upper limit of normal**
WBC	**white blood cells**
WT	**Weight**

PROTOCOL APPROVAL PAGE

Phase II Multicenter Study of **D**urvalumab and **O**laparib in platinum t**R**eated **A**dvanced triple negative breast cancer – **DORA**

Protocol Number: ESR-15-11311/EPM 6724
Protocol Version/ Date: V 6.0, 14Jun2021

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and in accordance with Good Clinical Practice (GCP).

I confirm that I have read the protocol and its attachments. I agree to conduct the described trial in compliance with

- This protocol, ESR-15-11311/EPM 6724,
- Good Clinical Practice guidelines (eg, ICH E6: Good Clinical Practice),
- Applicable regulatory requirements from the United States Code of Federal Regulations including 21 CFR parts 312 (Investigational New Drug [IND]), 50 (Protection of Human Subjects), 56 (institutional review board [IRB]), and 11 (electronic records and signatures).
- Country-specific regulatory requirements

Study Site Principal Investigator Name: _____

Study Site Principal Investigator Signature: _____

Date: _____

1 INTRODUCTION

Ten to twenty percent of invasive breast tumors are negative for all three predictive and prognostic immunohistochemical biomarkers—estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor 2 (HER2); these cancers are known collectively as triple negative breast cancer (TNBC).[1] Women with TNBC have an increased likelihood of distant recurrence and death as compared with women with other types of breast cancer.[2]

Breast cancer in the advanced stage remains an incurable disease, with general goals of therapy being to prolong survival, palliate symptoms, and optimize quality of life. In this disease setting, continuation of first-line chemotherapy results in a significantly improved overall survival (OS).[3] Whereas maintenance chemotherapy is desirable to prolong tumor responses, toxicities often limit its continuation.

The role of maintenance olaparib, a poly (adenosine diphosphate ribose) polymerase (PARP) inhibitor, has been explored in platinum-sensitive relapsed ovarian cancer; the median progression-free survival (PFS) and OS in subjects with Breast Cancer (BRCA) gene mutation on maintenance olaparib was significantly longer than that in the placebo group, with a tolerable toxicity profile.[4, 5] A significant proportion of TNBCs arise in BRCA mutation carriers[6, 7] and / or have gene expression profiles (basal-like) similar to that of BRCA-deficient tumors.[8] The therapeutic implication of this lies in exploiting synthetic lethality, resulting in disease control with favorable toxicity profile similar to that described in ovarian cancer.

The immune system can identify tumor-associated antigens and eliminate the cancerous cells expressing them; thus it plays an important role in combating tumor growth. However, tumor cells with reduced immunogenicity or an enhanced immunosuppressive mechanism contribute to the failure of the immune system in controlling tumor growth. Several factors may contribute to this failure, including expression of immune-inhibitory molecules, presence of immunosuppressive-regulatory T lymphocytes or immunosuppressive cytokines within the tumor microenvironment, and down-regulation of major histocompatibility molecules and tumor antigens leading to reduced antigen presentation and recognition.

The programmed death ligand-1 (PD-L1) is part of a complex system of receptors and ligands that are involved in control of T cell activation. In normal tissues, PD-L1 is expressed on T cells, B cells, dendritic cells, macrophages, and mesenchymal stem cells, as well in as a variety of non-hematopoietic cells. The normal function of PD-L1 is to regulate the balance between T cell activation and tolerance. Also expressed by tumors, PD-L1 acts at multiple sites; thereby, tumors evade detection and elimination by the host immune system. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing the target tumor cells and thus protecting the tumor from the immune system.

Recent studies have demonstrated high levels of tumor-infiltrating lymphocytes (TILs) in hormone-receptor negative and high grade tumors such as that of TNBC[9,10,11,12] as compared with hormone-receptor positive tumors. Increased levels of TILS has been associated with higher expression of PD-L1 messenger ribonucleic acid (mRNA)[13], which is significantly

higher in TNBC compared with non-TNBC.[14] This in turn has been correlated with improved prognosis in a number of cancers, suggestive of an important anti-tumor immune response. An anti-PD-L1 antibody could thus be used therapeutically to enhance anti-tumor immune responses in subjects with cancer. In addition, combining therapies with distinct, and potentially complementary, mechanisms of actions may further enhance the anti-tumor efficacy of each individual treatment.

In the context of advanced TNBC, the combination of PARP inhibition and PD-1 immune checkpoint inhibition is a therapeutic strategy worthy of further investigation.

Preclinical data (unpublished) suggests that those triple negative cell lines that are responsive to platinum chemotherapy are more likely to respond to the PARP inhibitor, olaparib. We hypothesize that olaparib either alone or in combination with the PD-L1 inhibitor will be efficacious in TNBC subjects who have responded to platinum-based chemotherapy.

1.1 Drug efficacy, safety and dosing: background

1.1.1 Olaparib in the context of breast cancer

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that has been approved as a monotherapy for treating patients with BRCA mutated advanced ovarian cancer following three or more prior lines of chemotherapy, it is also being developed both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. It is approved for use by both the European Commission (EC) and the U.S. Food and Drug Administration (FDA) in the treatment of women with BRCA-mutated advanced ovarian cancer. In January 2018, the FDA granted approval to olaparib tablets for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant or metastatic setting. This is based on data from OlympiAD, an open-label randomised phase III study investigating olaparib vs. physician's choice of chemotherapy (capecitabine, vinorelbine or eribulin) in patients with germline BRCA mutated, HER2 negative metastatic breast cancer.

Poly (adenosine diphosphate ribose) polymerase (PARP) inhibition is a novel approach that targets tumors with deficiencies in deoxyribonucleic acid (DNA) repair mechanisms. PARP enzymes are essential for repairing DNA single-strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double-strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as serous ovarian cancers and BRCA1 and BRCA2 breast cancers[15,16,17] cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib has been shown to inhibit selected tumor cell lines *in vitro* and in xenograft and primary explant models, as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Cells deficient in homologous

recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

PARP inhibitors such as olaparib may also enhance the DNA-damaging effects of chemotherapy.[16,18,19] For further information, please refer to the current version of the olaparib IB.

1.1.2 Preclinical experience with olaparib

Initial *in vitro* studies have identified olaparib as an effective agent in potentiating cell-killing by the alkylating agent methyl methanesulfonate[11]. Direct measurement of PARP-1 inhibitory activity in SW620 cell lysates identified the IC_{50} for PARP-1 inhibition to be around 6 nm, with total ablation of PARP-1 activity to be at concentrations of 30–100 nM.[11] The ability of olaparib to potentiate antitumor activity of temozolomide was further evaluated *in vivo* in animals bearing SW620-xenografted tumors. There was clear potentiation of temozolomide activity by olaparib, which was well tolerated when administered in combination.[11] Furthermore, cell lines that are deficient in homologous recombination as a result of non-functional BRCA1 or BRCA2 have been shown to be profoundly sensitive to PARP inhibition.[3,12]

1.1.3 Toxicology and safety pharmacology summary for olaparib

Olaparib has been tested in a standard range of safety pharmacology studies, eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioral, autonomic, or motor effects in the rats at the doses studied.[20]

Toxicology studies indicate that the bone marrow is the target organ of toxicity. In toxicity studies up to 6 months in rats and dogs, any changes in hematology parameters were fully or partially resolved upon withdrawal of the drug. Olaparib was found to have some mutagenic effects in rats that were to be expected given its primary target. There were no reproductive adverse effects in male rats, but fetal survival was decreased and fetal malformations increased, again to be expected given the primary pharmacology of olaparib.

Further information can be found in the current version of the olaparib Investigator's Brochure (IB).

1.1.4 Clinical experience with olaparib

Clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

The capsule formulation of olaparib was approved in December 2014 by the European commission (EC) for the indication: monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy. The United States (US) Food and Drug Administration (FDA) has approved olaparib capsules as monotherapy in patients with

deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The tablet formulation was registered for use in the US in August 2017 for ovarian cancer and in January 2018 for breast cancer. All ongoing studies, including the Phase III registration studies, are being performed with the tablet formulation. and the majority of patients treated with olaparib in AstraZeneca-sponsored clinical studies have received the tablet formulation.

As of 15 December 2018, approximately 10682 patients are estimated to have received olaparib in clinical programmes, investigator sponsored studies and collaborative group studies. An estimated 6956 subjects with ovarian, breast, gastric, pancreatic, and a variety of other solid tumors are estimated to have received treatment with olaparib across the dose range 10 mg once daily to 600 mg twice daily (bid) in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy or in combination with other chemotherapy/anti-cancer agents. Since 2012/2013, most new clinical studies have utilized the tablet formulation, which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 6108 patients in AstraZeneca-sponsored, interventional studies,1567 received the capsule formulation, 4516 received the tablet formulation, and 25 received both capsule and tablet.

The tablet formulation of olaparib (2 tablets bid) is considered much more subject-friendly; the tablet dose of 300 mg bid has been shown to demonstrate similar efficacy in terms of tumor shrinkage in BRCA-mutated ovarian cancer subjects as compared with the 400 mg bid capsule formulation—together with an acceptable safety profile.

The regulatory approval status of the tablet formulation of olaparib is as follows:

US: Approved in August 2017 for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer following response to platinum-based chemotherapy; and for the treatment of adult patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Approved in January 2018 for patients with deleterious or suspected deleterious germline BRCA mutated HER2 negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment.

EU indication: Approved in May 2018 as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Japan: Approved in January 2018 as maintenance treatment for adult patients with recurrent ovarian cancer who are sensitive to platinum based chemotherapy.

Emerging safety profile indicate that olaparib is generally well tolerated at monotherapy doses up to 400 mg bid (capsule formulation) and 300 mg bid (tablet formulation) in subjects with solid tumors. Administration of olaparib monotherapy has been associated with reports of laboratory findings and/or clinical diagnoses of:

- Hematological toxicity:
  - Anemia, (very common and of all CTCAE grades)
  - Neutropenia (common)
  - Lymphopenia (uncommon)
  - Thrombocytopenia (common)
  - Mean corpuscular volume elevation
  - Increased creatinine, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Nausea and vomiting, generally mild or moderate (CTCAE Grade 1 or 2), intermittent and manageable on continued treatment
- Stomatitis, generally mild or moderate (CTCAE Grad 1 or 2)
- Decreased appetite, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Diarrhea, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dyspepsia and upper abdominal pain, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dysgeusia, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dyspnea, very common, (CTCAE all grades)
- Fatigue (including asthenia), generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Headache, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dizziness, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Cough, generally mild or moderate intensity (CTCAE Grade 1 or 2

Myelodysplastic syndrome (MDS) and acute myeloid leukemia have been reported in <1% of subjects. The cases were typical of secondary MDS or therapy related acute myeloid leukemia. The duration of therapy with olaparib in subjects who developed secondary MDS or acute myeloid leukemia varied from <6 months to >2 years. All subjects had potential contributing factors for the development of MDS/acute myeloid leukemia, having received extensive previous chemotherapy with platinum agents. Many had also received other DNA-damaging agents.

New primary malignancies have been reported in a small number of subjects. There were other contributing factors or potential alternative explanations for the development of the new primary malignancy in all cases.

Pneumonitis events have been reported in <1% of subjects receiving olaparib. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of predisposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy).

1.1.5 Clinical experience with durvalumab

Durvalumab is an investigational human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass that inhibits binding of PD-L1 to PD-1 and CD80.

As of the Data cut-off (DCO) dates (12 July 2018), a total of 5127 subjects have been enrolled and treated in ongoing durvalumab clinical studies. Of these, 2229 patients received durvalumab monotherapy, 1573 patients received durvalumab in combination with tremelimumab, and 1325 patients received durvalumab in combination with an investigational and or an approved product. No studies have been completed or terminated prematurely due to toxicity.

Durvalumab has been given in ongoing studies as monotherapy or in combination with other drugs. The majority of safety data is based on the first-in-human single agent study in subjects with advanced solid tumors (Study 1108). Durvalumab was given intravenous (IV) every 2 or 3 weeks in a 3+3 dose escalation followed by expansion in 8 solid tumor types, one of which being TNBC. In the expansion cohort, durvalumab was given at a dose of 10 mg/kg IV every 2 weeks. Overall, the most frequently reported adverse events (AEs) were fatigue, nausea, dyspnea, decreased appetite, constipation, diarrhea, vomiting, cough, pyrexia, back pain, and rash. Approximately half of these AEs were Grade 1 to 2 in severity and manageable by general treatment guidelines. Grade 3 or higher AEs were noted in 35.9%. The events occurring in more than 1% of subjects were dyspnea (5.1%), increased gamma-glutamyltransferase (3.3%); fatigue, general physical health deterioration, increased aspartate aminotransferase, and back pain (2.3% each); anemia and dehydration (1.8% each); and abdominal pain vomiting, sepsis, syncope, and hypotension (1.3% each). No dose-limiting toxicities have been reported.

Efficacy data on durvalumab monotherapy in the expansion cohort was presented at American Society of Clinical Oncology (ASCO) 2014. With a median follow-up of 6 weeks, tumor shrinkage has already been seen in multiple tumor types. Durable responses have also been observed; this supports further development of durvalumab. Clinical assessments and subject enrollment are ongoing.

1.2 Research hypothesis

Preclinical data (unpublished) suggests that triple negative cell lines that are responsive to platinum chemotherapy are more likely to respond to the PARP inhibitor, olaparib. In the context of advanced TNBC, the combination of PARP inhibition and PD-1 immune checkpoint inhibition is a therapeutic strategy worthy of further investigation. We hypothesize that olaparib either alone or in combination with the PD-L1 inhibitor, durvalumab may be efficacious in TNBC patients who have responded to platinum-based therapy.

1.3 Rationale for conducting this study

Women with TNBC do not respond to estrogen/progesterone based endocrine therapy or other available targeted agents. Chemotherapy remains the mainstay of treatment. In the metastatic setting, these tumors are associated with a shorter median time to relapse and death compared to other metastatic breast cancer subtypes.[21] With the poorest prognosis of all breast cancer subtypes, this disease represents an important challenge and remains an unmet clinical need.

Over the last 5 years, potential targeted strategies for molecular subtypes of TNBC have been identified. A significant proportion of TNBCs (~30%) arises in BRCA gene mutation carriers or have gene expression profiles similar to BRCA deficient tumors representing a defective DNA damage repair system.[22,23] The therapeutic implication of this susceptibility has led to the development of synthetic lethality strategies such as treatment with polyADP-ribose polymerases (PARP) inhibitors such as olaparib. Furthermore, pathological studies have reported predictive and prognostic roles for the presence of TILs in hormone receptor negative and high-grade tumors such as advanced TNBC.[24,25] Consistent with these findings, multiple transcriptomic studies have identified TNBC subtypes characterized by altered expression of immune-response genes.[23] Several hypotheses for persistent disease despite chemotherapy and an active immune system response have been proposed, including masking of malignant cells by a variety of mechanisms, chronic antigen exposure, and "T cell exhaustion". A series of new immune-based therapies in which disruption of malignant cell masking by inhibition of CTLA-4 or PD-1/PD-L1 axes have entered the clinic. These have been studied in the context of several Phase 1 studies, which have reported significant promising clinical activity.[26,27,28] This clinical protocol assesses the activity of olaparib as well as the combination of olaparib and PD-L1 immunotherapy where two therapies with distinct and potentially complementary mechanisms of actions may further enhance anti-tumor efficacy.

1.4 Benefit/risk and ethical assessment

Data from the available pre-clinical studies and subsequent clinical development program demonstrate that olaparib appears to be active and generally well tolerated in subjects with solid tumors, including those with *BRCA*-mutated cancers. In ovarian cancer, responses have been seen in all subject groups, including platinum-resistant and refractory cancer.

From available studies, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure in subjects with advanced cancer.

Adverse laboratory findings and/or clinical diagnoses considered to be associated with administration of olaparib monotherapy include hematological effects (anemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache, dyspnea and dizziness. Most of these events were generally mild or moderate in intensity.

In a small number of subjects, pneumonitis, MDS/AML, and new primary malignancies have been observed. Evidence from across the development program for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are important potential risks for olaparib and are being kept under close pharmacosurveillance.

Identified risks with durvalumab are diarrhea, increases in transaminases, pneumonitis and colitis.

Potential risks include endocrinopathies (hypo- and hyper-thyroidism, hypophysitis and adrenal insufficiency), development of type 1 diabetes mellitus, hepatitis/hepatotoxicity,

neurotoxicities, nephritis, pancreatitis, dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, and immune complex disease. Further information on these risks can be found in the current version of the durvalumab IB.

1.5 Rationale for drug dosing in this study

1.5.1 Rationale for dose of olaparib

As of 15 December 2018, approximately 10682 patients are estimated to have received olaparib in clinical programmes, investigator sponsored studies and collaborative group studies. An estimated 6956 subjects with ovarian, breast, gastric, pancreatic, and a variety of other solid tumors are estimated to have received treatment with olaparib across the dose range 10 mg once daily to 600 mg twice daily (bid) in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. The recommended monotherapy tablet dose of olaparib is 300 mg bid. Olaparib is generally well tolerated at monotherapy doses of 300 mg bid (tablet formulation) in subjects with solid tumors. Toxicities such as hematological, gastrointestinal, eg, nausea, vomiting and diarrhea, anorexia, dysgeusia, fatigues, etc., are generally Grade 1 or Grade 2.

This study will use olaparib at the recommended monotherapy tablet dose of 300 mg bid.

1.5.2 Rationale for Durvalumab fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others.[29,30,31,32,33] Wang and colleagues investigated 12 monoclonal antibodies and found that fixed- and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies.[30.] In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters.[31]

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommended only for subjects with > 30kg body

weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (Appendix D).

1.5.3 Rationale for dose of olaparib in combination with durvalumab

A recent phase 1 study presented results for durvalumab therapy in combination with olaparib for ovarian cancer and TNBC, at the American Society of Clinical Oncology (ASCO) 2016. 10 ovarian cancer and 2 TNBC patients were included. Grade 3/4 adverse events included lymphopenia (2/12) and anemia (1/12). 1 PR (6 months) and 5 SD ≥ 4 months were seen in 9 evaluable patients, yielding a 67% disease control rate (DCR).[33]

Dosage of olaparib tablets 300 mg bid along with durvalumab 1500 mg Q4W was tolerated and efficacious in these patients who did not possess germline BRCA mutations, and is the recommended phase 2 dose (RP2D) employed in this study. [33]

2 STUDY OBJECTIVES

2.1 Primary objective

To determine the efficacy as assessed by PFS (based on RECIST 1.1) of maintenance olaparib or olaparib in combination with durvalumab following clinical benefit (complete response [CR], partial response [PR] or stable disease [SD]) with platinum based chemotherapy in the 1st or 2nd line setting for treatment of metastatic triple negative breast cancer (mTNBC).

2.2 Secondary objectives

- To determine the efficacy of maintenance olaparib following platinum based chemotherapy as assessed by overall survival (OS).
- To determine the efficacy of maintenance olaparib in combination with durvalumab following platinum based chemotherapy as assessed by overall survival (OS).
- To determine the safety and tolerability of maintenance olaparib.
- To determine the safety and tolerability of maintenance olaparib in combination with durvalumab.
- To determine the efficacy of maintenance olaparib following platinum-based chemotherapy as assessed by overall response rate (ORR) based on RECIST 1.1.
- To determine the efficacy of maintenance olaparib in combination with durvalumab following platinum-based chemotherapy as assessed by overall response rate (ORR) based on RECIST 1.1.
- To determine the efficacy of maintenance olaparib following platinum-based chemotherapy as assessed by clinical benefit rate (CBR) based on RECIST 1.1.
- To determine the efficacy of maintenance olaparib in combination with durvalumab following platinum-based chemotherapy as assessed by clinical benefit rate (CBR) based on RECIST 1.1.

2.3 Exploratory objectives

- To characterize the molecular epidemiology of biomarkers in TNBC through whole exome sequencing and immunohistochemistry studies.
- To explore the immune microenvironment of TNBC including, but not limited to, tumor-infiltrating lymphocytes (TILs), macrophages and others.

- To explore the tumor immunosuppressive microenvironment including but not limited to programmed death-ligand- 1 status on tumor and associated tissues.

- To analyze epigenetic changes in TNBC including, but not limited to, DNA methylation and non-coding RNAs such as miRNAs.

- To validate the role of minimally invasive blood-based markers such as circulating tumor cells or plasma DNA

- To perform mutational analysis on normal germline DNA obtained from blood samples and buccal swabs.

- Through systematic acquisition of tumor biopsies, additional tissue will be banked in the Duke Pathology central biorepository for future genetic research; it represents an invaluable resource toward achieving a deeper understanding of the mechanism of resistance or response to olaparib and or durvalumab.

- To compare patients randomized to olaparib and olaparib in combination with the durvalumab arm on their efficacy outcome measures.

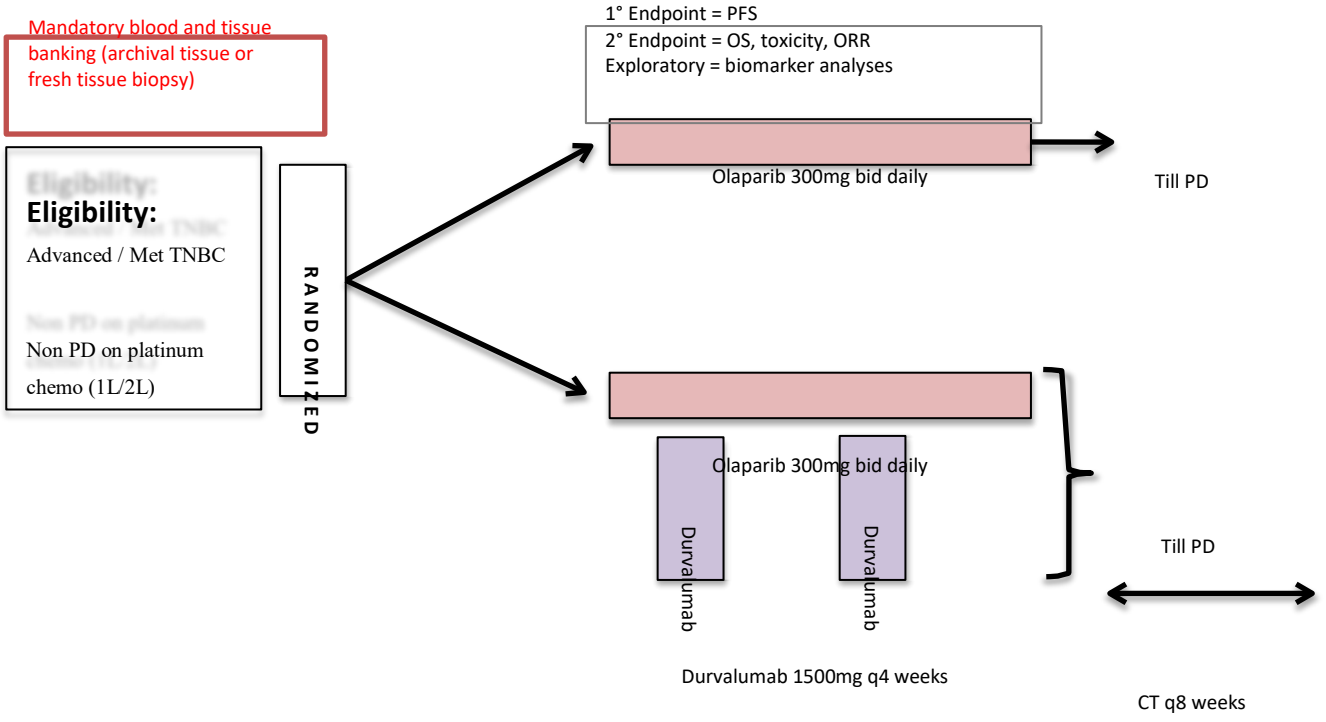
- To determine the efficacy as assessed by PFS, ORR, duration of response of maintenance olaparib in combination with durvalumab based on iRECIST criteria

3 STUDY DESIGN

3.1 Overall study structure and flow chart

This is a randomized, international, multicenter, Phase II study designed to explore the efficacy of olaparib or olaparib in combination with durvalumab in platinum-treated mTNBC (See Figure 1). The primary objectives are to explore olaparib or olaparib in combination with durvalumab as maintenance therapy following clinical benefit with platinum-based therapy in subjects with mTNBC.

Figure 1: Study Schema



Approximately 60 subjects with mTNBC who are receiving platinum-based chemotherapy and who have had no more than 2 lines of chemotherapy in the metastatic or advanced setting, with one of those being a platinum, will be enrolled. Subjects will be eligible for this study following a minimum of three 3-weekly cycles or six 1-weekly doses of platinum-based (cisplatin or carboplatin) chemotherapy as single agent or combination therapy as prescribed by their treating physician. Subjects can continue with further cycles of chemotherapy or be randomized any time after eligibility to allow for screening procedures to proceed without interruption of ongoing treatment. Subjects deriving clinical benefit (CR / PR / SD) with platinum-based therapy as determined by the treating physician will be eligible and randomized in a 1:1 ratio stratified by site and by the line of chemotherapy (in the metastatic setting). Randomization will be used to allocate subjects to either the olaparib or olaparib in combination with durvalumab arm, and comparisons between treatment regimens are planned as an exploratory objective. The purpose of randomization was to reduce bias due to subject selection into either treatment arm.

Germline BRCA mutation testing is not mandated for entry onto the trial; however, previous BRCA test data will be collected to ascertain the number of known BRCA mutation carriers -- which will be limited to 10 in total.

Tumor status will be evaluated as per RECIST v1.1 criteria. Tumor measurement for disease evaluation will be performed every 8 weeks on both arms, regardless of initial response to platinum chemotherapy. Estimation of PFS, duration of response and tumor response will be based on RECIST v1.1.

Following randomization, subjects will discontinue platinum chemotherapy and receive either olaparib tablets or olaparib in combination with durvalumab. Study treatment should commence following resolution of chemotherapy toxicities to CTCAE grade 2 or less and no more than 4 weeks after last dose of chemotherapy. Study treatment will continue until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination. Upon treatment discontinuation, subjects will be followed every 2 months for survival.

Safety will be evaluated on an ongoing basis in this study through the monitoring of all serious and non-serious adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAEv4.03).

3.2 Rationale for study design, doses and control groups

Subjects suitable for enrollment into this trial are adult subjects with histologically documented triple negative adenocarcinoma of the breast that is inoperable, locally advanced, or metastatic, and is not amenable to resection with curative intent, and who have received platinum-based chemotherapy in the 1st or 2nd line setting.

Randomization will be used to allocate subjects to either the olaparib or olaparib in combination with durvalumab arm, and comparisons between treatment regimens are planned. The purpose of randomization is to reduce bias due to subject selection into either treatment arm.

3.3 Rationale for prior treatment with platinum

The standard of care chemotherapeutic agent for unselected and advanced TNBC include taxane chemotherapy. A growing body of preclinical and clinical data suggests that platinum chemotherapy has a role to play in the treatment of both early and advanced TNBC, based on the hypothesis of greater susceptibility of TNBC to DNA-damaging chemotherapy agents. Clinical activity of the platinum combination (gemcitabine / cisplatin) has previously been evaluated with a response rate of around 30%[34]. The TNT trial evaluated 6 cycles of platinum therapy with monotherapy carboplatin dosed at area under the curve (AUC) 6 every 3 weekly in comparison to 6 cycles of taxane therapy with docetaxel dosed at 100mg/m2 every 3 weeks with the option of crossover upon treatment progression or toxicity in patients who had not previously received treatment for advanced TNBC. In the overall population, there was no difference between the ORR to carboplatin and to docetaxel 31.4% versus 34.0% (absolute difference -2.6%, 95% CI -12.1 to 6.9; p=0.66). There was no difference in median PFS 3.1 months (95% CI 2.4-4.2) versus 4.4 months (95% CI 4.1-5.1) or OS, 12.8 months (95% CI 10.6-15.3) versus 12.0 months (95% CI, 10.2-13.0) in both treatment groups. Patients with a

deleterious mutation in BRCA1/2 genes had a significantly better ORR to carboplatin than docetaxel (ORR 68% versus 33.3%; p=0.03). PFS was also longer 6.8 months versus 4.4 months; p=0.002. No difference was observed based on response to crossover treatment with the alternative drug. Thus platinum chemotherapy represents a widely used and appropriate therapy for subjects in the first / second line setting[35].

3.4 Inclusion Criteria

Subjects must meet all of the below criteria to be eligible for randomization and study treatment.

1. Age ≥ 21 years of age
2. ECOG performance status 0-2
3. Inoperable locally advanced or metastatic breast cancer not amenable to resection with curative intent and histologically confirmed to be estrogen receptor (ER) negative, progesterone receptor (PR) negative, and HER2 negative:
    - ER negative status is defined as < 1% tumor cells positive for ER by immunohistochemistry (IHC), irrespective of staining intensity
    - PR negative status is defined as < 1% tumor cells positive for PR by IHC, irrespective of staining intensity
    - NOTE: Enrollment is permitted for ER/PR low-expression subjects (defined as ≤ 10 %) who are expected to benefit from this trial at the investigator's discretion.
    - HER2 negative status is determined by:
        - IHC 1+, as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of invasive tumor cells, or
        - IHC 0, as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells, or
        - FISH negative based on:
            - Single-probe average HER2 copy number < 4.0 signals / cell, or
            - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals / cell

4. Minimum six 1-weekly doses or three 3-weekly doses of platinum chemotherapy (monotherapy or combination therapy at investigator's discretion) with stable disease (SD), partial response (PR) or complete response (CR) to the platinum therapy as assessed by investigator.
5. Has received no more than 2 prior chemotherapy lines for metastatic breast cancer including current platinum-based chemotherapy.
6. Able to provide a representative formalin-fixed, paraffin embedded tumor specimen archival or fresh tissue for correlative studies and biomarker analysis.
7. Hemoglobin ≥ 9.0 g/dL and no blood transfusions in the 28 days prior to study entry. Absolute neutrophil count ≥1,500/mm3. Platelet count ≥100 x 10^9/L.
8. Total bilirubin <1.5 x the upper limit of normal (ULN) with the following exception: subjects with known Gilbert's disease who have serum bilirubin <3 x ULN may be enrolled.
9. Aspartate transaminase (AST) and alanine transaminase (ALT) <2.5 x ULN with the following exceptions: subjects with documented liver or bone metastases may have AST and ALT <5 x ULN.
10. Alkaline phosphatase (ALP) <2 x ULN (<5 x ULN in subjects with known liver involvement and <7 ULN in subjects with known bone involvement).
11. Serum creatinine <1.5 x ULN or creatinine clearance >51 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.
12. For subjects of childbearing potential, agreement (by both subject and partner) to use two effective forms of contraception, including surgical sterilization, reliable barrier method, birth control pills, contraceptive hormone implants, or true abstinence and to continue its use for the duration of the study and for 3 months after last dose of study treatment.
13. Subjects of childbearing potential should have a negative urine or serum pregnancy test during their screening visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. Subjects willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examination.

15. For inclusion in genetic research, subjects must provide informed consent for genetic research collection of specimens to be stored at repository for future research.

3.5 Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled.

1. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of first dose of treatment. Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since last dose of the previous investigational agent of device.

2. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

3. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, or similar treatment) is not considered a form of systemic treatment.

4. Is taking chronic systemic steroids in doses > 10mg of prednisolone or equivalent within 7 days prior to the first dose of trial treatment.

5. Previous treatment with PARP inhibitors including olaparib.

6. Patients that have required discontinuation of treatment due to treatment-related toxicities from prior therapy with PD-1, PDL-1 or CTLA-4 inhibitors or previous history of immune-related grade 3 or 4 adverse event.

7. Known active central nervous system metastasis and / or carcinomatous meningitis. Subjects with previously treated brain metastases may participate, provided they have:

    a. Stable brain metastases [without evidence of progression by imaging (confirmed by computerized tomography {CT} scan if CT used at prior imaging) for at least four weeks prior to the first dose of trial treatment**,

    b. No evidence of new or enlarging brain metastases; any neurologic symptoms should have returned to baseline,

    c. Not used steroids for brain metastases in the 7 days prior to trial initiation. Taking chronic systemic steroids in doses ≤ 10mg of prednisolone is allowed.

**This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

8. History and/or confirmed pneumonitis, or extensive bilateral lung disease on high resolution/spiral CT scan.

9. Patients with suspected or confirmed myelodysplastic syndrome/acute myeloid leukemia.

10. History of another primary malignancy except for:

    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence.

    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.

    c. Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ.

11. Major surgery within 2 weeks of starting the study, and subjects must have recovered from any effects of any major surgery.

12. Receipt of radiation therapy within 4 weeks prior to starting study drug(s). Limited field of radiation for palliation within 2 weeks of the first dose of study treatment is allowed provided:

    a. The lung is not in the radiation field

    b. Irradiated lesion(s) cannot be used as target lesions

13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease, active bleeding diatheses including any subjects known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness / social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

14. Subjects unable to swallow orally administered medication, and subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.

15. Subjects requiring treatment with potent inhibitors or inducers of CYP3A4.

16. Pregnant or breast-feeding women. If breastfeeding can be stopped prior to study enrollment until 1 month after the last study dose, then the patient could be allowed to enter the study.

17. Immunodeficient subjects, eg, subjects who are known to be serologically positive for human immunodeficiency virus (HIV).

18. Received a live vaccine within 30 days of planned start of study therapy.

19. Subjects with a known hypersensitivity to olaparib or durvalumab, or any of the excipients of the product.

20. Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)

21. History of allogeneic organ transplant

22. Active bleeding diatheses

23. Patients with known active hepatic disease (ie, Hepatitis B or C)

24. Known history of previous clinical diagnosis of tuberculosis.

For procedures for withdrawal of incorrectly enrolled subjects, see Section 5.3.

3.6 Restrictions during the study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

3.6.1 Pregnancy/Breastfeeding

1. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use two highly effective methods of contraception (Table 1) from the time of screening and must agree to continue using such precautions for at least 1 month after the last dose of olaparib or at least 3 months after the last dose of durvalumab. Male partners of a female subject must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician.

2. Total sexual abstinence or engaging in sexual activity for the total duration of the trial and the drug washout period (1 month after the last dose) is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

3. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through at least 1 month after the last dose of olaparib or at least 3 months after the last dose of durvalumab. Not engaging in sexual activity for the total duration of the trial and the drug washout period (1 month after the last dose of olaparib or 3 months after the

last dose of durvalumab) is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period. Female partners of a male subject must use a highly effective method of contraception throughout this period.

4. Females of childbearing potential are defined as those who are not surgically sterile (*i.e.*, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).

5. Highly effective methods of contraception are described in Table 1. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 1: Highly Effective[a] Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[b]	• "Implants": Etonogestrel-releasing implants: eg, Implanon® or Norplant® • "Intravaginal Devices": Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg,NuvaRing® • "Injection": Medroxyprogesterone injection: eg, Depo-Provera® • "Combined Pill": Normal and low dose combined oral contraceptive pill • "Patch": Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra® • "Minipill": Progesterone based oral contraceptive pill using desogestrel: eg, Cerazette®

[a] Highly effective (ie, failure rate of <1% per year)

[b] This is also considered a hormonal method

[c] Cerazette® is currently the only highly effective progesterone-based pill

Contraception

Subjects with child-bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

- Condom with spermicide

and one of the following:

- Oral contraceptive or hormonal therapy (eg, hormone implants)
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

Total sexual abstinence. Abstinence must be prior to study enrollment, for the total duration of the study, and one month after last dose. Vasectomized sexual partner plus male condom, with participant assurance that partner received post-vasectomy confirmation of azoospermia

- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom+spermicide, provided coils are copper-banded

Acceptable hormonal methods:

** The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.**

- Etonogestrel implants (eg, Implanon, Norplan)+male condom with spermicide
- Normal and low dose combined oral pills+male condom with spermicide
- Norelgestromin/ethinyl estradiol transdermal system+male condom with spermicide
- Intravaginal device+male condom with spermicide (eg, ethinyl estradiol and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone-based pill.

3.6.2 Surgery

Olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle biopsy procedure.

3.6.3 Radiation

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator is not of the opinion that these are indicative of clinical disease progression during the study period. Full details of all these treatments are recorded in the subject's notes and appropriate section of the eCRF. Study treatment should be discontinued for a minimum of 3 days before the subject undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

3.6.4 Administration of other anti-cancer agents

Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Subjects may continue the use of bisphosphonates for bone disease and corticosteroids for the symptomatic control of brain metastases, provided the dose is stable in the last 7 days and does not exceed 10mg of prednisolone or equivalent.

.Full details of all of these treatments are recorded in the subject's notes and appropriate section of the eCRF.

3.6.5 Blood donation

Subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab, or until at least 3 days after the last administration of olaparib.

3.6.6 Other concomitant treatment and medications

1. No other chemotherapy specified outside of this protocol, hormonal therapy (hormone replacement therapy [HRT] is acceptable), or other novel agent is to be permitted during the course of the study for any subject (the subject can receive a stable low dose of corticosteroids during the study, as per exclusion criteria above).

2. Live virus and bacterial vaccines should not be administered while the subject is receiving study medication and during the 30-day follow-up period. An increased risk of infection resulting from administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs; the effects with olaparib are unknown.

3. Subjects should avoid concomitant use of drugs, herbal supplements, and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4, and consequently, this restriction is required to ensure subject safety.

4. Concomitant use of strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritonavir,

lopinavir/ritonavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) and moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole. Fosamprenavir, imatinib, verapamil) is not allowed.

5. Concomitant use of strong CYP3A inducers (eg, phenytoin, rifampicin, carbamazepine, St. John's Wort) and moderate CYP3A inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin) is not allowed.

6. Immunosuppressive medications should not be given concomitantly or given as a premedication prior to infusion. This includes but is not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-alpha (TNF-α) blockers.

   The following are allowed exceptions:
   - Use of immunosuppressive medications for the management of durvalumab-related AEs,
   - Short-term steroid premedication for patients receiving durvalumab if required for documented hypersensitivity reactions.
   - Use in patients with contrast allergies as a premedication/prep prior to scans.
   - In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.

7. Subjects who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted. The reason(s) for the use, doses, and dates of treatment should be recorded in the subject's medical records and appropriate section of the eCRF.

8. All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and that are different from the study medication must be documented.

3.7 Data Management

Data Management will be performed by Duke Clinical Research Institute (DCRI). DCRI is responsible for the development of a 21 CFR Part 11-compliant electronic data management system. This system will include eCRF screens, automated data validation checks and a randomization module. The data validation checks include checks for out-of-range and logically inconsistent data.

The DCRI will be responsible for medical coding. Adverse events will be coded using DCRI's current version of the medical dictionary for regulatory activities (MedDRA) updated semi-annually. The concomitant medications will be coded using DCRI's current version of the World Health Organization Drug Dictionary Enhanced (WHO DDE) updated semi-annually.

Protocol specific data management activities will be defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated and locked, a clean file will be declared.

3.8 Evaluation and calculation of variables

The primary efficacy outcome measure is as follows:

- PFS (progression free survival) defined as the time from randomization to the first occurrence of disease progression (as determined using RECIST 1.1 criteria and assessed by the Investigator) or death from any cause on study. Death on study is defined as death from any cause within 30 days of the last dose of study treatment regimen. Tumor progression will be assessed locally at each site by the investigators according to RECIST 1.1. No independent review of tumor progression is planned. PFS with disease progression determined by iRECIST for patients on the combination arm will also be examined in exploratory data analysis.

The secondary efficacy outcome measures in all subjects are as follows:

- OS (overall survival) defined as the time from entry onto trial until death from any cause.
- ORR (overall response rate) defined as the subjects achieving Complete Response or Partial Response as defined by RECIST 1.1.
- CBR (clinical benefit rate) defined as subjects achieving Complete Response, Partial Response or Stable disease ≥ 24 weeks

3.9 Calculation or derivation of efficacy variable(s)

The following definitions and criteria (from RECIST 1.1) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses. All measurements should be taken and recorded in metric notation, using a ruler or callipers. For the case of skin lesions, documentation (jpg file, preferred) by color photography, and a measurement with a ruler to estimate the size of the lesion, is recommended.

- **Measurable disease** - the presence of at least one measurable lesion.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter (LD) 20 mm using conventional techniques or 10 mm with spiral CT scan. Lymph nodes must be 15mm or greater (by spiral CT) in the shortest diameter to be considered measureable.

- **Non-measurable lesions** - all other lesions, including small lesions (LD <20 mm with conventional techniques or <10 mm, Lymph nodes <15mm SD with spiral CT scan), ie, bone lesions, ascites, pleural/pericardial effusion, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

Conventional CT should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

All imaging methods should be performed according to institutional standards with each subject having consistency of methods beginning from baseline through the course of the study.

3.9.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression and is determined as per Tables 10 and 11.

To be considered a response, CR or PR must persist for a minimum of 4 weeks. If, at the time of tumor response evaluation, either a PR or CR is observed, the same radiographic study should be repeated four weeks later for confirmation of response. After this confirmatory study, subjects should return to the schedule of evaluations as previously described.

4 STUDY PROCEDURES AND ASSESSMENTS

The schedule of assessments is provided in Appendix A. Descriptions of the scheduled evaluations are outlined below and complete information on study drugs and dosing is provided.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. This study will use local site labs for laboratory testing and for safety laboratory evaluations; biomarker specimens collected will be stored at study sites until end of study then shipped to the Duke Pathology central biorepository for future research.

4.1 Subject enrollment and randomization

4.1.1 Informed consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this clinical study for which they are volunteering to participate.

Before any study procedures are performed, potential subjects will have the outline of the study described to them, and they will be given a written informed consent document to read. If they consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel. Any subject who signs the

consent form will be considered a "screened" subject.

4.1.2 Screening Procedures

After written informed consent is obtained according to ICH GCP and local regulations, the subject's eligibility for the study and baseline disease status will be evaluated. This will occur in a screening visit during which the following will be evaluated and documented within 14 days prior to first dose of study drug(s).

Investigations, such as CT or MRI scans that have been performed as part of routine clinical practice, can be used as part of the screening process if performed within 28 days of first dose of study treatment; however, no non-standard of care investigations or tests that are study specific and required for screening may be performed prior to signature of the informed consent form.

The following baseline information should be obtained within 28 days prior to randomization:

- Demographic data and medical history, including previous and current diseases and medications, and confirmation of all prior treatments for metastatic breast cancer, including platinum based treatment requirements of investigator choice.
- Check availability of archival tumor tissue sample or new tumor biopsy if archival tissue unavailable
- Baseline adverse events to document pre-existing toxicity from prior treatment (assessed using CTCAE v4.03)
- Tumor response to platinum based chemotherapy, evaluation by CT or MRI (as defined by investigator assessment)
- Physical examination including the assessment of height, weight, pulse rate and blood pressure and BMI.
- Eastern Cooperative Oncology Group (ECOG) performance status
- Blood tests[b]
    - Full blood count (CBC with differential)
    - U&E: serum creatinine (SCr), urea, K+, Na+, glomerular filtration rate assessment
    - Liver function test: Bilirubin, ALP, AST/ALT, albumin
- Radiological investigations
    - CT or MRI scan to assess disease (thorax, abdomen and pelvis)
- Other tests
    - Pregnancy tests

See Appendix G for additional requirements for Korean sites only.

Where laboratory investigations have not been performed within the 7-day period prior to starting treatment, they must be repeated on day 1 of cycle 1.

4.1.3 Baseline documentation of "target" and "non-target" lesions

All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as ***target lesions*** and recorded and measured at baseline. Target lesions must be 10 mm in the longest diameter to qualify, or 15 mm in the short diameter for lymph nodes. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).

A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

4.1.4 Enrollment procedures

Subjects deriving clinical benefit (CR / PR / SD) with platinum-based therapy will be randomized to each of the treatment arms (olaparib or olaparib in combination with durvalumab) through the use of a stratified permuted block randomization in a 1:1 ratio to ensure within-stratum balance of characteristics between treatment arms. The stratification will be based on line of chemotherapy and by site. Randomization will be used to allocate subjects to either the olaparib or olaparib in combination with the durvalumab arm, and comparisons between treatment regimens are planned. The purpose of randomization is to reduce bias due to subject selection into either treatment arm.

There are five institutions participating as study sites in three countries including USA, Singapore, and South Korea. Each site will complete an eligibility checklist and enrollment must be submitted and approved prior to the randomization of any subject. The details of this procedure is provided in the site initiation materials.

4.1.5 Post-platinum chemotherapy tumor evaluation

Initial tumor assessment to assess for response to platinum chemotherapy will be performed as per standard of care following at least three 3-weekly (q21 day) or six 1-weekly doses of platinum chemotherapy. Attempts should be made to minimize time off treatment to less than 3 weeks. Any measurable disease must be documented at screening and re-assessed at tumor evaluation. Measurable disease is not required to go on study. Response assessments will be performed by the Investigator on the basis of physical examinations and imaging scans. Eligibility requires stable disease (SD), partial response (PR) or complete response (CR) per investigator assessment to the platinum therapy.

The same imaging method used at screening/baseline must be maintained throughout the study.

Computerized tomography (CT) scans are the preferred imaging modality for tumor assessments. Tumor assessments should include a diagnostic quality contrast-enhanced CT scan of the chest, abdomen, and pelvis at baseline. Computerized tomography (CT) scans of the neck should be included if there is clinically indication. Subsequent tumor assessments should include CT scans of the chest, abdomen, pelvis, and other known sites of disease. In addition to the

scheduled protocol scans, CT scans may be performed at the Investigator's discretion at any time if progressive disease is suspected.

In subjects for whom a CT scan is contraindicated because of an allergy to IV radiographic contrast, both CT scan of the chest without contrast and a magnetic resonance imaging (MRI) scan with contrast of the abdomen and pelvis and neck if clinically indicated are recommended; MRI scans may be performed in lieu of CT scans. Subsequent tumor assessments should include MRI scans of the chest, abdomen, pelvis, and other known sites of disease. The CT or MRI scans may be repeated at the Investigator's discretion at any time if progressive disease is suspected.

At the Investigator's discretion and if clinically indicated, other methods of assessment of measurable disease per RECIST 1.1 may be used (eg, brain scans using CT or MRI) in addition to those listed above. Additional procedures for tumor assessment should be performed as clinically indicated.

4.1.6 Procedures for randomization

Subjects with CR, PR, or SD by investigator assessment following minimum requirements in inclusion criteria of platinum-based chemotherapy are eligible to consent and complete screening activities. Subjects who meet all eligibility requirements will be randomly allocated to each of the treatment arms (olaparib or olaparib in combination with durvalumab).

Subjects will be allocated to each of the treatment arms (olaparib or olaparib in combination with durvalumab) through the use of a stratified permuted block randomization in a 1:1 ratio, to ensure within-stratum balance of characteristics between treatment arms. Randomization will be stratified by line of chemotherapy (1^{st} vs 2^{nd}) and by site.

4.1.7 Procedures for handling ineligible or screen-fail subjects

Subjects who signed the study informed consent form but are considered ineligible after screening will be considered as screening failures, and data will be handled as follows: The demographic information, informed consent, and inclusion/exclusion criteria will be collected for screen failure subjects. No other data will be collected for subjects who are screen failures unless the subject experienced a serious adverse event during the screening phase that is possibly related to a study procedure.

4.2 Treatments

Subjects will continue on study drug(s) until objective disease progression, as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

4.2.1 Identity of investigational product(s)

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib and the durvalumab to the Investigator/sponsor's dispensing vendor. This vendor will distribute drug supply to the participating sites.

Table 2: Identity of Investigational Product

Investigational product	Dosage form and strength
Olaparib	*150 mg oral tablet and 100mg oral tablet (100mg for dose reductions only)*
Durvalumab	*1500 mg intravenous*

[a] Descriptive information for olaparib can be found in the Investigator's Brochure

4.2.2 Olaparib

Olaparib (AZD 2281) (as film-coated tablet formulation) is intended for oral administration. The tablet monotherapy dose and the dose that will be used in this study is 300 mg bid taken continuously in 28 day cycles.

4.2.3 Olaparib: doses and treatment regimens

For all centers, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Olaparib will be dispensed to subjects on Day 1 and approximately every 28 days thereafter until the subject completes the study, the subject withdraws from the study or closure of the study.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

The effect of food on olaparib tablet has been investigated. Co-administration with food slowed the rate of absorption (tmax delayed by 2.5 hours and Cmax reduced by 20%), however food did not significantly affect AUC, therefore olaparib tablet formulation can be given without regard to food.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any subject enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the subject will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If longer than 2 hours after the scheduled dose time, the missed dose is not to be taken and the subject should take their allotted dose at the next scheduled time.

Subjects will continue with olaparib until objective disease progression (determined by RECIST) as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

4.2.4 Management of toxicity of olaparib

Any toxicity observed during the course of the study could be managed by interruption and/or dose reduction of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required for a maximum of 14 days on each occasion. If the interruption is any

longer than this, the sponsor or their designee must be informed. Olaparib must be interrupted until the subject recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03, grade 1 or less.

Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue treatment with olaparib.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs that the Investigator considers to be related to administration of olaparib.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the electronic case record form (eCRF).

Management of anemia

Adverse events of anemia CTCAE grade 1 or 2 (Hemoglobin [Hb] ≥8 g/dl) should be investigated and managed as deemed appropriate by the Investigator with or without interruption of study drug or change in dose, taking into account previous history of anemia. Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies, and hypothyroidism) should be excluded. In some cases, management of anemia may require blood transfusions. However, if a subject develops anemia CTCAE grade 3 (Hb <8 g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery, and the subject should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to ≥10 g/dl or baseline. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require Olaparib study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

If a subject has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood-transfusion dependent—as judged by the Investigator— study treatment should be permanently discontinued.

Management of neutropenia and leukopenia

An adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow-up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a subject develops febrile neutropenia, Olaparib study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of Olaparib study treatment.

Olaparib treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTC AE grade ≥1 (absolute neutrophil count

$\geq$1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step for a 300 mg monotherapy starting dose.

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the Investigator. If a subject develops thrombocytopenia CTCAE grade 3 or worse, study treatment should be interrupted for a maximum of 4 weeks. In some cases, management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of prolonged hematological toxicities while on study treatment

If a subject develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (absolute neutrophil count < 1 x 10^9/L)
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (platelets <50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct), and a peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the subject should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE. Study treatment should be discontinued if diagnosis of MDS is confirmed.

The dose of olaparib **must not** be adjusted under any other circumstances unless the site Principal Investigator (PI) has provided a prior agreement.

Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgment to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation

Toxicity	Study treatment dose adjustment
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Olaparib Dose reductions for study treatment

Initial Dose	Dose reduction 1	Dose reduction 2
300mg twice daily	250mg twice daily	200mg twice daily

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended, and a diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the site PI.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019, nausea was reported in 71% of the olaparib-treated subjects and 36% in the placebo-treated subjects; vomiting was reported in 34% of the olaparib-treated subjects and 14% in the placebo-treated subjects. These events are generally of mild to moderate (CTCAE grade 1 or 2) severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of treatment, with the incidence of nausea and vomiting not showing an increase over the treatment cycles. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, subjects should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines.

Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BD.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance $\leq$ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

Hepatic Impairment

If subsequent to study entry and while on study therapy, the patient develops hepatic impairment, the investigator should make every attempt to identify the underlying reason for the impairment.

Olaparib can be administered to patients with mild or moderate hepatic impairment (Child-Pugh Classification A or B) with no dose adjustment. Olaparib has not been studied in patients with severe hepatic impairment and is NOT recommended for use in these patients.

4.2.5 Durvalumab

Durvalumab should be given at least 1 hour after the subject has taken their olaparib morning dose. Durvalumab will be administered as an IV infusion over 60 minutes (+/- 5 minutes) at a dose of 1500 mg every 28 days.

Subjects allocated to the combination arm in the study will receive durvalumab via IV infusion at a dose of 1500 mg every 28 days in addition to olaparib tablets 300 mg bid. Treatment with durvalumab will commence on Day 1 of each 28 day cycles and will continue on the recommended schedule until progression of disease, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Disease progression requires confirmation, treatment with durvalumab will continue between the initial assessment of progression and confirmation of progression. If progression is not confirmed, then the subject should continue on study treatment and on treatment assessments.

4.2.6 Durvalumab: drug preparation

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab as a 500-mg vial solution for infusion after dilution**.** The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is

10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

For patients weighing >30 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) (based on an average body WT of 75 kg) should be prepared. For subjects ≤30 kg body weight, dose is determined using body weight, calculating the stock volume of durvalumab to achieve the accurate dose according to Appendix D. If a patient weighs exactly 30 kg or less, then patient should receive weight-based dosing for durvalumab.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab (ie, 30.0 mL for 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

4.2.7 Durvalumab: Doses and treatment regimens

Patient weight at baseline should be used for dosing calculations in patients ≤30 kg unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For patients ≤30kg, calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose according to Appendix D.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline, (possibly using dextrose as diluent) equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

Table 3: Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined above, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

4.2.8 Durvalumab: monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature, with maximum total time at room temperature not exceeding 8 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary. Following preparation of durvalumab, the

entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (+/- 5 minutes).

4.2.9 Management of toxicity of durvalumab

Durvalumab is an anti-PDL1 antibody that binds with high affinity and specificity to PD-L1 and blocks its binding to PD-1 and CD-80; thus, it promotes anti-tumor immunity and tumor-cell killing. Potential risks based on this mechanism of action of durvalumab and related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy, and pneumonitis. This class of drug has a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organ of the body.

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab.
- All dose modification should be documented with clear reasoning and documentation of the approach taken.

Immune-related adverse events

Based on the mechanism of action of durvalumab that leads to T-cell activation and proliferation, there is a possibility of observing immune-related AEs (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related. Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed and as described in Table 4.

Table 4: Durvalumab dose modification due to toxicity

See Appendix F for Toxicity Management Guidelines

In addition to the dose modifications shown, it is recommended the management guidelines for irAEs are followed; these modifications are presented in Table 5 below:

Table 5: Management of immune-related adverse events

1	Subject evaluation to identify any alternative etiology
2	In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
3	Symptomatic and topic therapy should be considered for low-grade events
4	Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
5	More potent immunosuppressors should be considered for events not responding to systemic steroids.

Pneumonitis

Pneumonitis has been reported with use of anti-PDL1 / anti-PD-1 antibodies. Initial work up should include a high resolution CT scan to rule out infection and pulse oximetry. Additional assessments are to include pulmonary function tests and blood gases. Pulmonary consultation is recommended. For Grade 2 pneumonitis that does not resolve to ≤Grade 1 within 3 days of maximal supportive care (including steroids) or ≥Grade 3 pneumonitis, permanently discontinue durvalumab.

Infusion Reactions

Subjects will be monitored during and after the infusion with assessment of vital signs (blood pressure [BP] and pulse) at the beginning of the infusion, every 30 minutes during the infusion, at the end of the infusion, and at 30 and 60 minutes in the 1-hour observation period post-infusion. If the infusion takes longer than 60 minutes, then BP and pulse measurements can be done more frequently if clinically indicated.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at
50% of the initial rate until completion of the infusion. If, following 4 hours of interruption, there is a persistent Grade 2 toxicity despite the use of appropriate medications such as antihistamines or paracetamol, then study treatment should be discontinued. If, following 4 hours of interruption, there is a decrease to Grade 1, then the drug may be re-introduced if it does not present an increased risk to the subject.

Hypersensitivity reactions

Hypersensitivity reactions, as well as infusion-related reactions, have been reported with anti-PDL1. As with any antibody, allergic reactions to dose administration are possible. Appropriate drug and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

Acute allergic reactions may occur, may be severe, and may results in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticarial, pruritus, angioedema, hypotonia, urticarial, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Hepatotoxicity

Increased transaminases have been reported during treatment with anti--PDL1.

Other AESIs observed with durvalumab include:

- Colitis
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

4.2.10 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach and sight of children. The label will include the dosing instructions to be reviewed at the time of dispensing.

The label will include the following information:

- Blank lines for quantity of tablets to be taken
- Date dispensed
- Instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

4.2.11 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage.

4.2.12 Treatment compliance

The patient will be provided with a diary in which each participant must record date and time

of each olaparib intake, reasons for any missed doses as well as any changes in dosing of study drug. Diaries will be provided to participants on Day 1 of cycle 1 and Day 1 (+/-2 days) of each

subsequent cycle. Diaries will be collected as source documentation at the end of each dosing cycles and at the EOT visit to document study drug administration for evaluation of treatment compliance. If the participant does not return the diary, delegated staff must evaluate and document dosing compliance.

The patient should return all boxes, bottles, blisters, and unused tablets of olaparib at the beginning of each new cycle (or at the end of each cycle). Any remaining or returned tablets will be counted by the Investigator or a designated person from his/her team and recorded.

If the patient does not bring the treatment dispensed at the previous visit back, the number of tablets taken will be estimated by the Investigator using the patient's diary and by questioning the patient. The patient will need to return the study drug at the next visit. The eCRF drug accountability data entered by the study site personnel into the electronic data capture (EDC) will be the data used by analysis.

Patients randomized to receiving durvalumab will receive treatment with durvalumab by study site staff at the study sites. Compliance will be assured by administration of the study treatment under the supervision of Investigator or his/her designee.

4.2.13 Accountability

Drug accountability will be the responsibility of the Investigator and/or the pharmacist. The Investigator and/or the pharmacist of the center and/or a designated person from the study team must maintain an accurate record of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, all study drugs will be reconciled and retained or destroyed according to local procedures and requirements. Destruction of unused therapeutic units will be performed according to standard modalities for that class of product. Destruction of study drugs should occur for product returned after drug accountability or after expiration date, or after the last visit of the last treated patient at the latest.

4.3 Discontinuation of study treatment

Subjects must be withdrawn from study treatment for the following reasons:

- At their own request or at the request of their legally acceptable representative (withdrawal of consent for treatment).
- At any time during study treatment and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the Investigator's opinion, continuation of study treatment would be harmful to the subject's well-being.
- Severe allergic reactions, such as exfoliate erythroderma, anaphylaxis, or cardio vascular collapse.
- Any other potential adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by either the Investigator or a designated associate(s).
- Substantial non-compliance with study procedures.
- Subjects with a beta human chorionic gonadotropin test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event (SAE)
- Use of illicit drugs or other substances that may, in the opinion of the Investigator or a designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Development of any intercurrent illness or situation that would, in the judgment of the Investigator, affect assessments of clinical status and study endpoints to a relevant degree.
- Subjects should discontinue study treatment if confirmed disease progression occurs. If the treating physician feels that the subject will receive clinical benefit from continued study treatment despite progression, the subject may remain on study drug after consultation with the study PI. However, the subject will be considered as having progressive disease, as per the RECIST 1.1 criteria
- Subject lost to follow-up
- The date of the last dose of the second study drug is considered as the date of the end of the study treatment
- Permanent discontinuation of a specific study drug should be declared by the site treating physicians

In all cases, the reason for withdrawal from treatment must be recorded in the case report form (CRF) and in the subject's medical records.

4.4 Procedures for discontinuation of a subject from investigational product

A subject whose treatment is permanently discontinued due to an adverse event or clinically significant laboratory value must be followed up as per institutional practice until resolution or stabilization of the event, whichever comes first.

An end of treatment (EOT) visit should be conducted within 30 days of the last dose of the study drug or within 30 days of the decision to permanently discontinue the study drug. If the subject withdraws from the study at a scheduled visit, the EOT assessment can be performed on that day. (See section 4.5.3 for visit details)

Any subject who has not progressed at the time of discontinuation of study treatment will continue to have tumor assessments performed every 8 weeks until disease progression, initiation of subsequent anticancer therapies or death, whichever comes first.

Upon treatment discontinuation, subjects will be followed every 2 months for survival. Completion of the survival follow-up period will occur once the last subject in the Extension period discontinues study treatment, or the Extension period reaches one year of duration, whichever comes first.

4.5 Collection of study variables

The site Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. Data will be entered into the electronic case report form (eCRF) of a web-based data management system. Site personnel will be trained and responsible for entering data specified in the protocol into the eCRF according to the eCRF Instructions. Site personnel will provide their site local laboratory lab normal range values during the data management system set-up. When all data has been entered, reviewed, and source data verification completed; the site PI will be notified to sign the eCRF electronically.

4.5.1 During olaparib or olaparib and durvalumab maintenance

Cycle 1 Day 1

The following assessments will be done prior to administration of maintenance treatment:

- Physical examination
- ECOG performance status
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology
- Blood chemistry

- Liver function tests
- Thyroid function tests for combination arm only (thyroid stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxine (T4))
- Electrolytes
- Correlative blood samples for translational studies
- Assess adverse events (AE)
- Record concomitant medication
- Dispense olaparib or olaparib and administer durvalumab

See Appendix G for additional laboratory requirements for Korean sites only.

4.5.2 Subsequent visits

Subsequent visits with study doctor should occur once every 28 days +/- 3 days for Cycle 2 onward. More frequent visits are permitted if clinically indicated.
While the following assessments will continue to be performed, they will only be done for clinical purposes. These data will no longer be entered into the study database:

- Physical examination
- ECOG performance status
- Vital signs (weight, temperature, blood pressure, respiration, pulse)
- Hematology and Chemistry per tables 6 and 7 that follow:

Table 6. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Table 7. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alanine aminotransferase	Thyroid stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxine (T4)) (combination arm only)
	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

See Appendix G for additional laboratory requirements for Korean sites only.

4.5.3 End-of-study visit

When it has been determined that a subject should be removed from treatment, she will be asked to return for a treatment termination visit, which should preferably occur within 30 days after her last administration of study drug. Wherever possible, this visit should also be undertaken by subjects who withdrew from the study prematurely. All subjects will be followed for a minimum of 30 days after the last dose of olaparib/durvalumab.

If a subject is removed from the study due to drug-related adverse events, the subject will be followed until resolution of any drug-related AE occurring during the study or within 30 days of the last olaparib/durvalumab dose, or for 30 days, whichever is longer. In the presence of toxic effects, follow-up visits will be required every four weeks until all study-related toxicities have resolved to baseline (or <Grade 1 per CTCAE), have stabilized or are deemed irreversible.

The following assessments will be made during the end of study visit:

- Physical examination (including oral/tympanic temperature and body weight)
- ECOG performance status
- Vital signs (systolic and diastolic blood pressure, pulse rate).

- Clinical laboratory profile (hematology, biochemistry and liver function test) per tables 6 and 7
- Radiological disease status assessment at Investigator's discretion

- Serious Adverse Events recording

The only data to be entered into the eCRF from this visit will be the End of Treatment reason, radiological disease status assessment (if applicable), and Serious Adverse Event (if applicable).

4.6 Biological sampling procedures

The volume of blood that will be drawn from each subject in this study is as follows:

Table 8: Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**Frequency of Sampling**	**Total volume (mL)**
Safety	**Clinical chemistry**	3	Once at the start of each cycle	18 (for 6 cycles)
	Hematology	3	Once at the start of each cycle	18 (for 6 cycles)
Biomarker		30	At predefined time points	120 (4 time points)

Total	36	156

4.6.1 Handling, storage and destruction of biological samples

Serial blood samples will be collected from all patients. Please refer to Appendix A for schedule of assessment for sampling time points and table 9 for blood volume to be collected. All blood samples will be collected by either direct venipuncture or an indwelling central venous catheter. Complete instructions for blood sample processing, handling and shipment will be provided in the Laboratory Manual.

4.6.2 Biomarker samples

The specific description of collection, handling and shipment of these samples is described in a separate Correlative Science Lab Manual.

Related to biomarker blood sample collection, specifically, the sites will collect blood at visits C1D1, D1 after each staging cycle (C3D1, C5D1, C7D1 etc), and EOT; please refer to the Schedule of Assessments (Appendix A) for further detail.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop collection or not perform or discontinue an analysis due to either practical or strategic reason (e.g. inadequate sample number, issues with quality of sample, issues with assays etc.). Depending on the results obtained during the study, sample collection and/or analysis may be omitted at the discretion of the study chair. If a decision is made by study chairs to stop collection of blood samples, notification will be provided to every investigator in writing.

4.6.3 Withdrawal of informed consent for donated biomarker samples

As collection of the biomarker samples is an integral part of the study, if the subject withdraws consent from the study, the study team will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analysed at a later date or as required by local regulations. If a patient withdraws consent for the study, the investigator must make every effort to determine the primary reason for this decision and record this information. Subjects may decide to stop biomarker collection but continue on study. This does not constitute withdrawal of consent for the entire study.

4.7 Follow-up procedures

30-day safety follow-up

All subjects will have safety evaluations for 30 days following the last dose of the study treatment. AEs will be assessed until 30 days following the last dose of olaparib and/or durvalumab. All concomitant medications given to a patient as a result of an SAE experienced during this period will be recorded. All cancer medications/therapies given to a subject ≤30 days after the last dose of olaparib/durvalumab must be recorded. Subjects lost to follow-up should be recorded as such.

Disease progression follow-up

Any subject who has not progressed at the time of discontinuation of study treatment will continue to have tumor assessments performed every 8 weeks (+/- 7 days) until disease progression, initiation of subsequent anticancer therapies or death, whichever comes first.

Survival follow-up

Upon completion of the 30-day safety follow-up or disease progression follow-up, all subjects except those who died, withdrew consent or were lost to follow-up will be followed for survival every 8 weeks (+/- 7 days) until death. Completion of the survival follow-up period will occur once the last subject in the Extension period discontinues study treatment, or the Extension period reaches one year of duration, whichever comes first.

4.8 Efficacy

The first disease evaluation for subjects following start of olaparib or olaparib in combination with durvalumab will occur at week 8 +/- 7 days. Subsequent to the first tumor evaluation, disease status and tumor response will be assessed per RECIST using standard CT/MRI scans in eight-week intervals (+/- 7 days) until disease progression as defined by RECIST 1.1 or as clinically indicated.

For subjects who discontinue any of the study drug due to toxicity in the absence of confirmed objective progression, objective tumor assessments should be continued every 8 weeks (+/- 7 days) for until confirmed objective disease progression.

If study subject is on durvalumab, disease progression requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progressive disease (PD) in the absence of clinically significant deterioration. Treatment with olaparib and durvalumab will continue between the initial assessment of progression and confirmation for progression. Subjects with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible to continue to receive study drug.

4.8.1 Efficacy outcome measures

Only response evaluation per RECIST will be entered into eCRF for the Extension period.

The primary efficacy outcome measure is as follows:

PFS, defined as the time from randomization to the first occurrence of disease progression (as determined using RECIST v1.1 criteria and assessed by the Investigator) or death from any cause on study. Death on study is defined as death from any cause within 30 days of the last dose of study treatment regimen. Tumor progression will be assessed locally at each site by the investigators according to RECIST 1.1. No independent review of tumor progression is planned. PFS with disease progression determined by iRECIST will also be examined in exploratory data analysis for the combination arm. The secondary efficacy outcome measures in all subjects are as follows:

- OS (overall survival) defined as the time from randomization until death from any cause.

- ORR (overall response rate) defined as the subjects achieving Complete Response or Partial Response as defined by RECIST 1.1.

- CBR (clinical benefit rate) defined as subjects achieving Complete Response, Partial Response or Stable disease ≥ 24 weeks

Methods of measurement

The following definitions and criteria (from RECIST 1.1) should be used for the baseline evaluations of existing disease and for the ongoing evaluation of tumor responses. All measurements should be taken and recorded in metric notation, using a ruler or callipers. In the case of skin lesions, documentation by color photography and a measurement with a ruler to estimate the size of the lesion is recommended.

- **Measurable disease** - the presence of at least one measurable lesion.

- **Measurable lesions** – non-lymph node lesions that can be accurately measured in at least one dimension with LD 20 mm using conventional techniques or 10 mm with spiral CT scan, or 15mm for lymph nodes with spiral CT.

- **Non-measurable lesions** - all other lesions ie, bone lesions, ascites, pleural/pericardial effusion, including lesions that do not meet the measureable criteria above.

- Conventional CT should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

All imaging methods should be performed according to institutional standards with each subject having consistency of methods beginning from baseline through the course of the study.

Table 9: Response criteria

Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the nadir (smallest sum) LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all target lesions
Stable Disease (SD)	Persistence of one or more non-target lesion(s)

Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression and is determined as per Table 10 below.

Table 10: Definition of best overall response as per RECIST criteria

Target lesions	Non-Target lesions	Evaluation of New lesions	Overall response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

To be considered a response, CR or PR must persist for a minimum of 4 weeks. If, at the time of tumor response evaluation, either a PR or CR is observed, the same radiographic study should be repeated 4 weeks later for confirmation of response. After this confirmatory study, subjects should return to the schedule of evaluations as previously described.

5 SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

5.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be a symptom (eg, nausea, chest pain), sign (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be used to report AEs for this study.

5.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase that fulfils one or more of the following criteria:

- Results in death not related to breast cancer disease progression
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the Investigator(s) and documented or reported on the SAE eCRF page.

5.3 Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Only AESIs meeting serious criteria will be reported during the Extension period.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Chair.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

5.4 Recording of adverse events

For the Extension period, only SAEs will be reported in eCRFs. Non-serious AEs will be

managed according to the site's clinical practice and the toxicity management guidelines set forth in this protocol, but will not be reported in eCRFs.

Information about all SAEs, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected and recorded and followed as appropriate.

All SAEs, whether or not deemed drug-related, must be reported within IBM-CD (eCOS) by the site Investigator or qualified designee within 1 business day of first becoming aware of the event.

Questions about SAE reporting can be referred to DCRI Safety Surveillance at 1-**919-668-8624, or at 1-866-668-7799 within North America.**

If the IBM-CD system is temporarily unavailable, the event, including the Investigator-determined causality to study drug, should be reported via a paper back-up SAE form to DCRI Safety Surveillance. Upon return of the availability of IBM-CD system, the SAE information must be entered into IBM-CD.

The following variables will be collected in the eCRF during the Extension period for each SAE:

- SAE (verbatim per CTCAE)
- The date when the SAE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Investigator causality rating against the Investigational Product (yes or no) /combination drug (yes/no)
- Action taken with regard to investigational product /combination agent
- Outcome
- Date AE met criteria for serious AE
- Reason AE is defined as serious (fatal or life threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant, requires inpatient hospitalization or prolongation of existing hospitalization).
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to additional study drug

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 5.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

5.4.1 Time period for collection of adverse events and serious adverse events

All SAEs will be collected during the extension period through 30 days after the last dose of either drug or until the initiation of an alternative anticancer therapy. Please refer to the Schedule of Assessments in Appendix A.

5.5 Follow-up of unresolved serious adverse events

All SAEs should be treated appropriately. Such treatment may include changes in study drug treatment, including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an SAE is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

5.6 Adverse events based on signs and symptoms

When collecting SAEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.7 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, for vital signs should only be reported if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as the event and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an SAE

Cases where a subject shows an AST **or** ALT ≥3xULN **and** total bilirubin ≥2xULN may need to be reported as SAEs, please refer to Section 5.3 (AESI definition) for further instructions.

5.8 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. SAEs due to progression will be reported and classified as unrelated to treatment.

5.9 New cancers

The development of a new primary cancer should be regarded as an SAE since this event will generally meet at least one of the serious criteria (see Section 5.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the subject into the study. These do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

5.10 Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used, mTNBC, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

5.11 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death that is clearly the result of disease progression should be documented in the eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the main or primary event causing the death must be documented in the eCRF as a SAE within **1 business day** (see Section 5.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be included within the eCRF.

5.12 Other events requiring reporting

5.12.1 Pregnancy

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the sponsor or their designated representatives within 1 business day, ie, immediately, but **no later than 1 business day** of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

5.12.2 Reporting of serious adverse events

SAEs are reported with the eCRF database within 1 business day of the investigator's knowledge of the event.

***** The investigative site must also indicate, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the site Principal Investigator.

5.12.3 Translational study

Biopsies and tissue specimen

At time of enrollment, all archival or fresh tissue obtained will be banked. This will be a requirement for participation in the study. Where possible, formalin-fixed paraffin embedded (FFPE) blocks are preferred. If blocks are unavailable, thirty unstained and unbaked 5-µm slides from each subject (minimum of 10 slides for pre-treatment biopsy/archival tissue required) should be processed as close to batch shipment date as possible. Post-treatment biopsy is encouraged but optional. All tissue will be banked at the site until the batch shipment date near full enrolment of the trial. Each sample will be labelled with Subject ID code and the required number of slides retained / shipped to the relevant research laboratories. All blood, tissue samples and buccal swabs will be processed centrally by the Duke BioRepository & Precision Pathology Center (BRPC). Shipping back to the Duke BioRepository & Precision Pathology Center (BRPC) will be arranged and communicated to the sites nearing the end of enrollment. Please see lab manual for further details.

All study subjects will have a buccal swab for germline DNA collected during screening; these will banked at study sites until the end of the study.

Immunohistochemical HRD assay

Banked tumor samples will be profiled based on protein expression using multiplexed microscopy. The multiplexing ability of the Opal-Vectra system will be used to study different antibody combinations relevant to homologous recombination for all samples obtained in this

study.

Whole exome sequencing (WES)

DNA samples will be obtained from the tumor samples and from the buccal DNA swabs that will be obtained during screening. PCR-based exon sequencing will be performed using standard techniques. Genetic variants will be characterized as missense, nonsense, and frameshift, and then will be narrowed by retaining only somatic rare variants and homozygous mutations. Wald testing will initially be used to define relationships between gene alterations and response to therapy.

We also have a very large set of profiled primary and metastatic TNBC samples (both carboplatin sensitive and insensitive) that will serve as a comparator set for the samples in this proposal (Blackwell, SABCS, 2013). We will be able to use this established and well-characterized set for quality control and gene mutation comparison.

Immune profiling

Immune profiling will be done using standard immunohistochemistry techniques. The following immune markers will be stained and quantitated using an experienced breast pathologist who will quantitate staining in tumor and in the stroma. The following markers will be assessed initially:

1. Quantitative TILs using H and E stained slide[21]
2. CD4
3. CD8
4. FoxP3 (SP97)
5. Anti PDL-1 (E1L3N)

Modifications to the immune markers may be made depending on emerging evidence.

6 ETHICAL AND REGULATORY REQUIREMENTS

6.1 Ethical conduct of the study

This trial will be conducted in compliance with this protocol, Good Clinical Practice guidelines (eg, ICH E6: Good Clinical Practice or Singapore Guideline for Good Clinical Practice [SGGCP]), and applicable national and local regulatory requirements.

The site Principal Investigator shall ensure that personnel involved in the conduct of this study are qualified by education, training, and experience to perform their respective tasks. The site Principal Investigator has ultimate responsibility for trial conduct at the site.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

6.2 Subject data protection

Subjects will be assigned unique code numbers and will not be identified by name. Subject confidentiality is held strictly in trust by the participating Investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to genetic and biological sample tests, in addition to the clinical information relating to participating subjects.

The sponsor will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain study staff might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the medical monitor or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

6.3 Ethics and regulatory review

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to prospective subjects. The Investigator should also provide the IRB/IEC with a copy of the product labelling information to be provided to prospective subjects, along with any updates.

The Investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to local and national regulatory requirements or institution procedures.

6.4 Informed consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this clinical study for which they are volunteering to participate.

Before any study procedures are performed, potential subjects will have the outline of the study described to them, and they will be given a written informed consent document to read. If they consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel. Any subject who signs the consent form will be considered a "screened" subject.

6.5 Changes to the protocol and informed consent form

Should amendments to the protocol and/or informed consent document be required, the amendments will be written by the sponsor and provided to the Investigator for submission to

their IRB/IEC.

6.6 Protocol deviations

Protocol deviations (noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), Manual of Procedures or requirements) will be noted in Site Monitoring reports. Of note, noncompliance may be either on the part of the participant, the site Investigator, or the study site staff. Sites are expected to develop and implement corrective actions promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be promptly reported to the sponsor or their designee.

All deviations from the protocol must be addressed in study subject source documents. Protocol deviations must be reported to the local IRB/IEC per local guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

6.7 Publication policy

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, Investigators will not be allowed to perform subset analyses at any point before the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the sponsor/investigator.

7 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

7.1 Statistical analyses and determination of sample size

Based upon current standard of care,[30] the median PFS (mPFS) in this population is estimated to be approximately 2 months, and a clinically relevant improvement with either of the proposed maintenance treatments would be to an mPFS of 4 months. In both arms of the study, it is proposed to test a null hypothesis of an mPFS of 2 months against an alternative hypothesis of an mPFS of 4 months. To test this hypothesis, assuming an exponential PFS distribution, use of an exponential MLE test, a two-sided significance level of 5% and a power of 90%, 25 subjects are required per arm. To allow for a drop-out rate of approximately 20%, the sample size per arm will be inflated to 30 subjects, for a total of 60 subjects.

Comparison between the two treatment arms will be performed as an exploratory analysis.

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7.2 Safety data review committee

Accruing vital status, progression, and safety data will be reviewed by the committee comprising the Dora Study Chair, Study Co-Chair and Correlative Science Chair; one of the Study Chairs will serve as the bi-monthly committee meeting leader. The DCRI statistician will serve as the meeting secretary and will provide agreed-upon statistical reports in advance of the committee meeting. The Safety Data Review Committee's primary goal is to determine if there is a clear

early difference between the Arms A and B in terms of safety, efficacy, or risk-benefit. The Safety Data Review Committee may invite opinions from the study site investigators, intermittently, and will consider stopping either one, or both, arms if the safety profile is unacceptable. The committee will meet together and review rates of deaths, SAEs, and progressions approximately every 2 months until all subjects have been accrued. A written committee charter will provide guidance regarding meeting conduct; the DCRI statistician and the meeting Chair will jointly prepare summary minutes from each meeting and circulate for review by the committee members.

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9 APPENDICES

Appendix A : Schedule of Assessments

Extension period – please refer to sections 4.5.2 and 4.5.3 for data to be entered in eCRF.

SCHEDULE OF ASSESSMENTS					
Procedures	Screening[p]	Cycle 1 (q28)	Cycle 2 (q28) onwards	End of treatment	Follow-up
	Within 14 days	D1	D1 (+/- 3 days)	Within 30 days	Every 8 weeks (+/- 7 days)
Informed consent	X				
Inclusion/exclusion criteria check	X				
Demographics	X				
Past medical history including past cancer chemotherapy, radiotherapy and surgery	X				
Archival tumor tissue sample	X[b]				
Tumor assessment (CT or MRI)[c]	X		X[d]		X[d]
Complete physical examination	X	X	X	X	
Weight (with height at screening)	X	X	X		

Vital signs[e]	X	X[e]	X[e]	X	
AE and toxicities	X	X	X	X[f]	
Concomitant medications	X	X	X	X	
ECOG performance status	X	X	X	X	
Hematology[g]	X	X[n]	X	X	
Chemistry and electrolyte[h]	X	X[o]	X	X	
Liver panel (ALT/AST/Bilirubin)[i]	X	X[n]	X	X	
GFR assessment[j]	X	X[n]	X	X	
Pregnancy test[k]	X				
Buccal Swab for DNA analysis	X				
Biomarker blood tests[l]		X	X *[after staging, at alternating Cycles 3,5,7, etc]*	X	
Optional tumor biopsy[m]	X[l]			X[m]	
If CR/PR/SD:					
Randomization	X				
Olaparib		300 mg BID daily			
If randomized to combination arm:					
Durvalumab IV 1500 mg		X	X		
Survival assessment[n]					X[n]

NOTE: Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within the screening window (Day-14 to Day -1) may be used for the study. Investigations, such as CT or MRI scans that have been performed as part of routine clinical practice to assess response to platinum, can be used as part of the screening process if performed within 28 days of first dose of study treatment. Screening assessments are to be performed within 14 days preceding cycle 1 day 1 unless otherwise noted. Except for cycle 1 day 1, all other study visits and assessments during the treatment period should be performed within +/- 3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations and unforeseen delays. All assessments and procedures to be performed pre-dose unless otherwise specified.

[a] The end of treatment visit should occur approximately 30 days after the last administration of olaparib or durvalumab

whichever is discontinued last, or until initiation of another therapeutic regimen.

[b] Archival tissue (either formalin fixed paraffin embedded tumor specimens or a minimum of 10 unstained paraffin slides) must be available prior to entry into the study. In the absence of archival tissue, fresh tissue biopsy samples, excluding cytology and fine needle aspiration specimens are acceptable.

[c] Tumor assessments performed according to RECIST version 1.1 The method used for a patient (CT or MRI) must be the same throughout the study.

[d] Tumor assessment performed every 8 weeks starting on Days 21-28 of Cycle 2 and every 8 weeks (+/- 7 days) thereafter until documented disease progression. The results should be reviewed prior to dosing at the next cycle; tumor assessments should be performed < =7 days prior to continuation of study treatment on Day 1 of the subsequent cycle.

[e] Includes heart rate, systolic and diastolic blood pressure whilst in a seated position, and temperature. On durvalumab dosing days, recorded prior to dosing and at the end of the infusion.

[f] Patients with unresolved adverse events or serious adverse events will be followed until the event is resolved or stabilized, the patient is lost to follow-up or it has been determined that the study treatment or participation is not the cause of the event.

[g] Includes RBC count, WBC count, WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes and other cells), absolute neutrophil count, hemoglobin, hematocrit and platelet count.

[h] Includes sodium, potassium, chloride, bicarbonate urea, creatinine, calcium, phosphorus, magnesium, thyroid stimulating hormone (combination arm only), free triiodothyronine (T3) (combination arm only) and free thyroxine (T4) (combination arm only). See Appendix G for additional required tests for Korean sites only.

[i] Includes total bilirubin, total protein, albumin, AST, ALT and alkaline phosphatase.

[j] As calculated by the Cockcroft-Gault formula.

[k] For women of childbearing potential (including those who have had a tubal ligation). For all other women, documentation must be present in medical history confirming the patients is not of childbearing potential.

[l] Biomarker blood specimens will be collected at visit C1D1, D1 after each staging cycle (C3D1, C5D1, C7D1 etc), and End of Treatment (EOT).

[m] Tumor biopsy collection is optional for study participation if archival tissue is available. For patients who consent for tumor biopsy, this will be collected prior to treatment, and/or during interval of clinical response, at the time of progression and/or at the end of the study.

[n] Information about survival and subsequent anti-cancer therapies will be collected via telephone calls, patient medical records and or clinic visits approximately every 8 weeks until death, loss to follow-up, or study termination unless the patient requests to be withdrawn from follow-up; this request must be documented and signed by the investigator.

[o] Where laboratory investigations have not been performed within the 7-day period prior to starting treatment, they must be repeated on day 1 of cycle.

[P] ECG is required at screening for Korean sites only. See Appendix G.

Appendix B : Known Strong in Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3Aa	Strong Inducers of CYP3Ae
Boceprevir	carbamazepin[ef]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazoleb	
ketoconazoleb	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

Source:
FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo
Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Study Chair of the protocol.
a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Appendix C : Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drugs? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either "yes" or "no":

No = There is no reasonable possibility that the event may have been caused by study drugs.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject's clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drugs.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix D : Under 30 kg Total Body Weight Durvalumab Dose calculation

Dose Calculations ONLY for subjects 30kg body weight and under. ALL subjects over 30kg total body weight are given fixed dosing of 1500mg every 4 weeks (see section 1.5.2)

1. Ordered dose: 20 mg/kg

2. Subject weight: X kg

3. Dose for subject: Y mg = 20 (mg/kg) × X (kg)

4. Dose to be added into infusion bag:

Dose (mL) = Y mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL)/10.0 (mL/vial)

Example for 30kg subject dosing at 20mg/kg every 4 weeks:

1. Ordered dose: 20 mg/kg every 4 weeks

2. Subject weight: 30 kg

3. Dose for subject: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag: Dose (mL) = 600 mg/50 (mg/mL) = 12.0 mL

5. The theoretical number of vials required for dose preparation:

Number of vials = 12.0 (mL)/10.0 (mL/vial) = 2 vials

(provided by Astra Zeneca)

Appendix E : Assessment of Possible Drug Induced Liver Injury

The following assessments are to be reported in the clinical database, utilizing Comment Form as necessary for additional information.

• Subject's age, sex, weight, and height

• Signs and symptoms related to hepatotoxicity: type and timing to exposure

• Relationship of exposure duration and dose to the development of the liver injury

• Pertinent medical history • Concomitant drugs with dates and doses • Pertinent physical exam findings

• Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)

• Time course of serum enzyme and bilirubin elevations (consider tabular and/or graphical display of serial laboratory data)

• A summary of all available clinical information including, if known:

− Prior or current history of ethanol use

− Presence of risk factors for NASH (e.g., obesity, diabetes, marked hypertriglyceridemia) 16 Contains Nonbinding Recommendations

− Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease, prestudy AT values, if available

− Symptoms and clinical course including follow-up to resolution − Special studies (i.e., ultrasound, radiologic examinations, liver biopsy results)

− Presence or absence of possible confounders, including concomitant illness, use of concomitant drugs that are known hepatotoxins, such as acetaminophen

• Treatment provided

• Dechallenge and rechallenge results, if done

• Outcomes and follow-up information

• The site should also supply redacted copies of available hospital discharge summaries, pathology and autopsy reports

Appendix F : Toxicity Management Guidelines Durvalumab

These guidelines are now provided to sites as a separate document.

Appendix G : Additional required tests (Korean sites ONLY)

4.1.2 Screening Procedures

- 12 lead resting ECG
- Amylase, Lipase, GGT (gamma glutamyl transferase), Urinalysis

4.5.1 During olaparib or olaparib and durvalumab maintenance

- Amylase, Lipase
- As clinically indicated: GGT, Urinalysis

4.5.2 Subsequent visits (and Table 7. Clinical chemistry Serum or Plasma Laboratory Tests)

- Amylase, Lipase
- As clinically indicated: GGT, Urinalysis

Urinalysis Tests[a]

Bilirubin

Blood

Glucose

Ketones

pH

Protein

Specific gravity

Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells